

产品名称: **BMS-378806**

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| 生物活性:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |           |            |            |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
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| Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | BMS-378806 is a potent HIV-1 attachment inhibitor that interferes with CD4-gp120 interactions. BMS-378806 selectively inhibits the binding of HIV-1 gp120 to the CD4 receptor with EC50 of 0.85-26.5 nM in virus.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |           |            |            |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
| IC <sub>50</sub> & Target                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HIV[1]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |           |            |            |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
| In Vitro                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p>In a series of biochemical assays, BMS-378806 is not an effective inhibitor of HIV integrase, protease, or reverse transcriptase, but did compete with soluble CD4 binding to a monomeric form of gp120 in an ELISA assay with IC50=100 nM. The specificity of BMS-378806 toward inhibition of HIV-1 is confirmed by evaluation against HIV-2, SIV, MuLV, RSV, HCMV, BVDV, VSV, and influenza virus, with no significant inhibitory activity observed at concentrations ranging from 10 to 30 μM and no overt cytotoxicity toward the host cells, CC50&gt;225 μM. BMS-378806 is not a potent inhibitor of any of the five major human CYP isoforms, evaluated as recombinant preparations, with IC50 values of &gt;100 μM for CYP1A2 and CYP2C9, 23 μM for CYP2C19, 20 μM for CYP2D6, and 39 to 81 μM for CYP3A4. Moreover, since BMS-378806 is metabolized by CYP450 1A2, 2D6, and 3A4, it is unlikely to lead to severe drug–drug interactions in a clinical setting[1]. BMS-378806 inhibits viral replication by interfering with the binding interactions of gp120 with the cellular CD4 receptor. The IC50s determined for the gp120s from HIV LAI, BAL, NA420LN40, SF162, NL4-3, NA420B33, YU2, AD8, JRCSF, and 92US15.6 are 0.1, 0.1, 0.3, 0.5, 0.6, 0.7, 0.9, 1.0, 1.1, and 1.6 μM, respectively. A similar observation is also made for BMS-378806 (IC50s range from 0.2 to 9.6 μM)[2]. BMS-378806 binds directly to gp120 at a stoichiometry of approximately 1:1, with a binding affinity similar to that of soluble CD4. The potential BMS-378806 target site is localized to a specific region within the CD4 binding pocket of gp120 by using HIV-1 gp120 variants carrying either compound-selected resistant substitutions or gp120-CD4 contact site mutations[3].</p> |           |            |            |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
| In Vivo                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <p>In toxicology studies, BMS-378806 is well tolerated in rats at doses of 100 mg/kg/day for 2 weeks and in dogs at doses of 90 mg/kg for 10 days. The dose-proportional increases in the AUC and C<sub>max</sub> are observed between doses of 5 and 25 mpk, when BMS-378806 is administered either in the solution or suspension formulation. In all three species, plasma levels of drug exceeded the concentrations required to half-maximally inhibit virus replication in vitro. The volume of distribution of BMS-378806 ranges from 0.4 to 0.6 L/kg, indicative of partitioning beyond plasma; however, examination of brain levels in the rat reveals minimal CNS penetration[1].</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |           |            |            |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
| <p><b>In Vitro:</b></p> <p><b>DMSO : ≥ 50 mg/mL (123.02 mM)</b></p> <p>* "≥" means soluble, but saturation unknown.</p> <table><tr><th rowspan="2">Preparing<br/>Stock Solutions</th><th>Solvent<br/>Concentration</th><th>Mass</th><th>1 mg</th><th>5 mg</th><th>10 mg</th></tr><tr><th>1 mM</th><td>2.4604 mL</td><td>12.3022 mL</td><td>24.6045 mL</td></tr><tr><th rowspan="2"></th><th>5 mM</th><td>0.4921 mL</td><td>2.4604 mL</td><td>4.9209 mL</td></tr><tr><th>10 mM</th><td>0.2460 mL</td><td>1.2302 mL</td><td>2.4604 mL</td></tr></table> <p>*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。</p> <p>储备液的保存方式和期限 -80°C, 6 months; -20°C, 1 month。 -80°C 储存时，请在 6 个月内使用， -20°C 储存时，请在 1 个月内使用。</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |           |            |            | Preparing<br>Stock Solutions | Solvent<br>Concentration | Mass | 1 mg | 5 mg | 10 mg | 1 mM | 2.4604 mL | 12.3022 mL | 24.6045 mL |  | 5 mM | 0.4921 mL | 2.4604 mL | 4.9209 mL | 10 mM | 0.2460 mL | 1.2302 mL | 2.4604 mL |
| Preparing<br>Stock Solutions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Solvent<br>Concentration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Mass      | 1 mg       | 5 mg       |                              | 10 mg                    |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 mM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2.4604 mL | 12.3022 mL | 24.6045 mL |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 5 mM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.4921 mL | 2.4604 mL  | 4.9209 mL  |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 10 mM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.2460 mL | 1.2302 mL  | 2.4604 mL  |                              |                          |      |      |      |       |      |           |            |            |  |      |           |           |           |       |           |           |           |

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| <p><b>Solvent&amp;Solubility</b></p> | <p><b><i>In Vivo:</i></b></p> <p>请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 <b>In Vitro</b> 方式配制澄清的储备液，再依次添加助溶剂：</p> <p>——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline<br/>Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.15 mM，饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 400 <math>\mu</math>L PEG300 中，混合均匀向上述体系中加入 50 <math>\mu</math>L Tween-80，混合均匀；然后继续加入 450 <math>\mu</math>L 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-<math>\beta</math>-CD in saline)<br/>Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.15 mM，饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 20% 的 SBE-<math>\beta</math>-CD 生理盐水溶液中，混合均匀。</p> <p>3.请依序添加每种溶剂： 10% DMSO →90% corn oil<br/>Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.15 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 玉米油中，混合均匀。</p> |
| <p><b>References</b></p>             | <p>[1]. Wang T, et al. Discovery of 4-benzoyl-1-[(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)oxoacetyl]-2-(R)-methylpiperazine (BMS-378806): a novel HIV-1 attachment inhibitor that interferes with CD4-gp120 interactions. J Med Chem. 2003 Sep 25;46(20):4236-9.</p> <p>[2]. Ho HT, et al. Envelope conformational changes induced by human immunodeficiency virus type 1 attachment inhibitors prevent CD4 binding and downstream entry events. J Virol. 2006 Apr;80(8):4017-25.</p> <p>[3]. Guo Q, et al. Biochemical and genetic characterizations of a novel human immunodeficiency virus type 1 inhibitor that blocks gp120-CD4 interactions. J Virol. 2003 Oct;77(19):10528-36.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>实验参考：</b></p>                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><b>Animal Administration</b></p>  | <p>Rats, Dogs and Monkeys[1]</p> <p>The pharmacokinetic properties of BMS-378806 in the rat, dog, and cynomolgus monkey are summarized. The oral bioavailability of BMS-378806 in rats, administered as a solution in PEG 400/EtOH (90:10 v/v), is 19% at a dose of 5 mg/kg while an aqueous crystalline suspension of free base in 0.75% (w/w) Methocel A4M Premium administered orally at the same dose afforded a relative bioavailability of 61%.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>Kinase Assay</b></p>           | <p>To measure gp120-CD4 binding, the wild-type or variant gp120 proteins are first captured onto a plate by D7324 antibody. CD4 binding is initiated by adding sCD4 to a gp120-coated plate. To determine the ability of BMS-378806 to compete with sCD4 for gp120 binding, the compound is added simultaneously with sCD4 and reactions are carried out in buffer C (50 mM Tris-HCl [pH 7.5], 100 mM NaCl, 1% bovine serum albumin) for 2 h at room temperature. After washing with buffer B (20 mM Tris-HCl, 500 mM NaCl, 0.05% Tween 20 [pH 7.5]), the bound CD4 is detected with OKT4</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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|                   | antibody (0.36 $\mu$ g/mL) and goat anti-mouse peroxidase conjugate. Bound antibody is detected with 3,3',5,5'-tetramethylbenzidine chromogenic substrate for peroxidase[3].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>References</b> | <p>[1]. Wang T, et al. Discovery of 4-benzoyl-1-[(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)oxoacetyl]-2-(R)-methylpiperazine (BMS-378806): a novel HIV-1 attachment inhibitor that interferes with CD4-gp120 interactions. J Med Chem. 2003 Sep 25;46(20):4236-9.</p> <p>[2]. Ho HT, et al. Envelope conformational changes induced by human immunodeficiency virus type 1 attachment inhibitors prevent CD4 binding and downstream entry events. J Virol. 2006 Apr;80(8):4017-25.</p> <p>[3]. Guo Q, et al. Biochemical and genetic characterizations of a novel human immunodeficiency virus type 1 inhibitor that blocks gp120-CD4 interactions. J Virol. 2003 Oct;77(19):10528-36.</p> |



源叶生物